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08/852,495	05/07/1997	DAVID A. RUDDY	8907-057-999	7064

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/852,495	RUDDY ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,53-55,59-64,100,102-107,110-112,114-119 and 123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,53-55,59-64,100,102-107,110-112,114-119 and 123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed June 23, 2004. Currently, claims 49, 53-55, 59-64, 100, 102-107, 110-112, 114-119, 123 are pending.

2. This action is Final.

3. This action contains new grounds of rejection necessitated by amendment.

4. Any objections and rejections not reiterated below are hereby withdrawn.

a. Pease has been withdrawn in view of the arguments directed to the CGXXXXCG arguments. However, applicant argues that the claims encompass 2 allelic forms and the complements thereof. This argument has been thoroughly reviewed, but is not found persuasive because the claims are directed to SNP which are found in a population with about 25% or less frequency. Thus, based upon the instant specification, it is clear that the 'wild-type' allele is present in the populations at greater than 25% frequency and would not be encompassed by the claims.

b. With respect to the 103 rejection previously of record over Claims 100, 102, 123, the amendments to the claims that require that the oligonucleotide does not hybridize to SEQ ID NO: 1 overcomes the rejection, as the cited nucleic acid was SEQ ID NO: 1. The response asserts that a TD would overcome this rejection. This argument has been thoroughly reviewed, but is not found persuasive because the statute in fact requires "(3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor

under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c)." The instant application does not appear to contain an oath or declaration under 1.130.

Priority

5. This application claims priority to CIP 08/724,394, filed October 1, 1996. However, the 08/724,394 case does not appear to provide any disclosure of polymorphisms at particular positions. Therefore, the instant application is awarded the benefit of the instant filing date, namely May 7, 1997.

Drawings

6. The drawings are acceptable.

New Matter

7. Claims 100, 102-107, 110-112, 114-119, 123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP 2173.05(i) provides, "Any negative limitation or exclusionary proviso must have basis in the original disclosure." Any claim containing a negative limitation

which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

In the amended claims, reference to "an oligonucleotide that selectively hybridizes to the target sequence under conditions in which the oligonucleotides does not hybridize to SEQ ID NO: 1 or a complement thereof" are included. The amendment proposes that the new claim language clarifies the issue. However, the specification does not describe or discuss "an oligonucleotide that selectively hybridizes to the target sequence under conditions in which the oligonucleotides does not hybridize to SEQ ID NO: 1 or a complement thereof". Instead the specification describes SEQ ID NO: 1 is the nucleotide sequence in the HH subregion from an unaffected individual. SEQ ID NO: 2 is the nucleotide sequence of an affected individual (page 5). The response asserts that the invention provides 397 new polymorphic sites in the region of the HH gene (Table 1). This description does not support an oligonucleotide that selectively hybridizes to the target sequence under conditions in which the oligonucleotides does not hybridize to SEQ ID NO: 1 or a complement thereof. There are no teachings in the instant specification of sequence that hybridize to the mutant, but not the normal sequence. There are no conditions or any sequences provided which would support such a recitation. The concept of "an oligonucleotide that selectively hybridizes to the target sequence under conditions in which the oligonucleotides does not hybridize to SEQ ID NO: 1 or a complement thereof" does not appear to be part of the originally filed invention. Therefore, "an oligonucleotide that selectively hybridizes to the target

sequence under conditions in which the oligonucleotides does not hybridize to SEQ ID NO: 1 or a complement thereof" constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112- Written Description

8. Claims 100, 102-107, 110-112, 114-119, 123 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to one or more oligonucleotides comprising a sequence that hybridizes under stringent conditions to a SNP in a target nucleic acid at a SNP site selected from a group consisting of a SNPs at positions 230376, 214795, 207400, 200027, 195404, 16007, 125581, 120853, 96315, 61465, 40431, 328526 and 35983.

The specification teaches that SEQ ID NO: 1 is a nucleotide sequence of approximately 235 KB in the HH subregion from an unaffected individual. The specification teaches that the 397 new polymorphic sites in the region of the HH gene are listed in Table 1. The polymorphisms are taught to provide surrogate markers for use in diagnostic assays to detect the likely presence of the mutations 24d1 and/or 24d2 (page 11, lines 32-38). An HH affected individual was sequenced between D6S2238 and D6S2241 (page 24). The specification teaches that a subset of the

polymorphic alleles so defined were further studied to determine their frequency in a collection of random individuals.

The specification teaches that the SNP at 35983 (an A to G change) was present in the ancestral chromosome and rare in the random DNAs. A genotyping of 90 HH patients revealed that 79.4% of the patients has a C at this position as compared to 5% in the random DNAs (page 28). 85/90 patients assayed contained identical 24d1 and 35983 (C182.1G7T/C genotypes).

Further, the specification detections a change at 61,465 which is a G to A change) (page 28). 76 patients contained a T at 61,465 as compared with 5% in random individuals. 75.5% of affected individuals contained a T.

Table 2 demonstrates that the frequency of the SNPs in random chromosomes. This measurement provides no indication of the frequency of the SNPs in diseased or HH patients.

As provided in the Written Description guidelines, Example 9, claims drawn to oligonucleotides which hybridize under stringent conditions absent functional language have not been described. The skilled artisan would expect substantial variation among species encompassed within the scope of the claims because stringent conditions would not yield substantially similar DNAs. A representative number of species has not been disclosed since the stringent conditions are not in combination with the function of DNA. The claims as written do not contain any particular length limitation on the oligonucleotides. The claim would encompass oligonucleotides which are homologs, variants, splice variants and the "wild type" previously disclose by applicant.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant has defined only a fragment of a nucleic acid sequence. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Response to Arguments

The response traverses the rejection. The response asserts that thee functional characteristics of selective hybridization have been added to the claims. This argument has been reviewed but is not convincing because hybridization is not functional language, but rather further defines the structure of the nucleic acids. The hybridization

language is intended to further limit the way the nucleic acid looks rather than the biological activity of the nucleic acid.

Further, the claims are not commensurate in scope with the arguments. The claims are not directed to a nucleic acid which hybridizes to SEQ ID NO: 2 and not to SEQ ID NO: 1. Rather the claims are directed to a nucleic acid oligonucleotide which hybridizes to a portion of SEQ ID NO: 2 but not to full SEQ ID NO: 1. Thus, as noted in the newly added rejections under 102, the claims do not narrow the scope such that they do not encompass sequences which were not contemplated at the time the invention was made. Specifically, the lepidopteran sodium channel taught by Kreitman is encompassed by the instant claims, but does not appear to be disclosed in the instant specification. Therefore, the teachings in the specification of a species of nucleic acids is not representative of the genus encompassed by the claims.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 49, 53-55, 59-68, 100, 102-107, 110-112, 114-119, 123 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated polynucleotides of 10 nucleotides in length and isolated polynucleotides of at

least 18 consecutive bases which span SNP 35983 and 61465, does not reasonably provide enablement for an isolated polynucleotide spanning 230376, 214795, 207400, 200027, 195404, 16007, 125581, 120853, 96315, 40431, 38526. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to nucleic acids which span a SNP within SEQ ID NO: 1 or SEQ ID NO: 2 wherein the SNP is located at one of the recited positions and is found in a general population with about 25% or less frequency.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied

three or more times, only 6 have been consistently replicated. Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The art teaches that presence of SNPs in the same gene does not indicate that each of the SNPs is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Additionally, Ioannidis teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Guidance in the Specification.

The specification teaches that SEQ ID NO: 1 is a nucleotide sequence of approximately 235 KB in the HH subregion from an unaffected individual. SEQ ID NO: 2 is a nucleotide sequence from an affected individual. The specification teaches that the 397 new polymorphic sites in the region of the HH gene are listed in Table 1. The polymorphisms are taught to provide surrogate markers for use in diagnostic assays to

detect the likely presence of the mutations 24d1 and/or 24d2 (page 11, lines 32-38). An HH affected individual was sequenced between D6S2238 and D6S2241 (page 24). The specification teaches that a subset of the polymorphic alleles so defined were further studied to determine their frequency in a collection of random individuals.

The specification teaches that the SNP at 35983 of SEQ ID NO: 1 (an A to G change) was present in the ancestral chromosome and rare in the random DNAs. A genotyping of 90 HH patients revealed that 79.4% of the patients has a C at this position as compared to 5% in the random DNAs (page 28). 85/90 patients assayed contained identical 24d1 and 35983 (C182.1G7T/C genotypes).

Further, the specification detections a change at 61,465 which is a G to A change) (page 28). 76 patients contained a T at 61,465 as compared with 5% in random individuals. 75.5% of affected individuals contained a T.

Table 2 demonstrates that the frequency of the SNPs in random chromosomes. This measurement provides no indication of the frequency of the SNPs in diseased or HH patients.

The skilled artisan would not know how to use each of the polynucleotides in the claims, since the specification fails to provide an association of the SNPs at positions 230376, 214795, 207400, 200027, 195404, 16007, 125581, 120853, 96315, 40431, 38526 with any particular disease or condition. Thus, the skilled artisan would be unable to practice the claimed invention with out further experimentation.

Working Examples

There are no working examples in the specification directed specifically to 10 of the particular SNPs recited, namely 230376, 207400, 200027, 195404, 16007, 125581, 120853, 96315, 40431, 38526.

Quantity of Experimentation

The skilled artisan would be required to perform additional undue experimentation to determine whether SNPs at positions 230376, 207400, 200027, 195404, 16007, 125581, 120853, 96315, 40431, 38526 would be useful for any particular means. The specification specifically asserts that these SNPs are "surrogate markers for use in diagnostic assays to detect the likely presence of the mutations 24d1 and/or 24d2." There is no teachings in the specification that SNPs at position 230376, 207400, 200027, 195404, 16007, 125581, 120853, 96315, 40431, 38526 would be useful as surrogate markers for known markers. There is no evidence in the specification that SNPs at positions 230376, 207400, 200027, 195404, 16007, 125581, 120853, 96315, 40431, 38526 are useful for any particular means. Moreover, the explicit teachings in the specification indicate that SNPs at 35983 and 61465 are more frequently seen in diseased patients. The evidence provided for each of these SNPs does not confer a use for the other 10 SNPs in which no association or demonstration of association with a disease or usefulness as a surrogate marker. The art clearly establishes that the general knowledge in the art concerning SNPs and polymorphisms is such that an association of a SNP with a disease does not provide an indication that all SNPs also confer the same association, see discussion above. The art teaches that the replicability of association studies on small studies is not predictable in addition to evidence that SNPs in the same gene do not have the same associations.

The skilled artisan would be required to perform undue experimentation to determine how to use the method for detecting a polymorphism which is not associated in any particular manner with a disease or condition. Moreover, the claims are written so broadly as to require the skilled artisan to determine whether the polymorphisms are

associated with additional diseases without a reasonable expectation of success. While one could conduct additional experimentation to determine whether e.g. the presence of a SNP at position 230376, 207400, 200027, 195404, 16007, 125581, 120853, 96315, 40431, 38526 might be associated with, e.g. HH, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue.

It is also unclear from the specification how the skilled artisan would use an oligonucleotide containing an A or G at position 35,983 of SEQ ID NO: 1. The instant specification appears to indicate in Table 2 that the nucleic acid T appears in 95% of the random chromosomes and C appears in 5% of the random chromosomes. Therefore, it is unclear how the skilled artisan would use a sequence which does not appear to occur in the random chromosome population. The specification fails to assert any use for the alleles aside from T and C at position 35,983 of SEQ ID NO: 1. Moreover, the instant specification fails to address the same concern for position 61465 of SEQ ID NO: 1. Thus, the skilled artisan would not know how to use the claimed oligonucleotides which have not been shown to exist in nature.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the association of polymorphisms in small samples with particular diseases is not reproducible. The factor of unpredictability weighs heavily in favor of undue experimentation. Further, the specification provides insufficient guidance since the

specification fails to provide any teachings that SNPs at 230376, 207400, 200027, 195404, 16007, 125581, 120853, 96315, 40431, 38526 is associated with any particular disease, namely HH. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that In re Wands applies to whether undue experimentation is require to practice the invention, however the Office Action is drawn to whether the claimed invention would be found useful. This argument has been thoroughly reviewed, but is not found persuasive because enablement relates to both methods of making and using the claimed invention. As provided in MPEP 2164, "The enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent." In the instant case, the specification has not taught the skilled artisan how to use the claimed oligonucleotides. The claimed oligonucleotides are asserted to be "surrogate markers for use in diagnostic assay to detect the likely presence of the mutation 24d1 and/or 24d2, preferably 24d1, in homozogotes or heterozygotes" however, as discussed

above, there is no teachings in the specification that each of these polymorphic SNPs are in fact surrogate markers. The skilled artisan would be required to perform additional, undue and unpredictable experimentation to determine whether these markers are surrogate markers for 24d1 or 24d2 or both or neither. The response asserts that "the haplotypes defined by the polymorphic sites of Table 1 are predictive of the likely presence of the HH gene mutation 24d1" (response page 9). This argument has been thoroughly reviewed, but is not found persuasive because it is unclear what haplotype is being referred to. It is unclear whether the haplotype refers to the entire combination of alleles present in SEQ ID NO: 2. This is not commensurate in scope with the claimed invention. Table 1 comprises 5 pages, over 100 alleles within SEQ ID NO : 2. It is unpredictable that each of these markers is a surrogate for mutations at 24d1. There is no evidence of record that each of these markers are surrogates for a mutation which is associated with a disease. The mere presence of low frequency in a general population does not support the concept of surrogates. The specification merely suggests that the polymorphic sites of Table 1 are predictive of the likely presence of the HH gene mutation 24d1. This assertion does not appear to state that they are predictive. The statement is not evidence that they are predictive. Thus, additional undue and unpredictable evidence would be required to determine whether each of the polymorphic sites are predictive of a mutation which is indicative of a disease.

The response asserts that the likelihood of a carrier of the ancestral gene mutation carrying a combination of two, three or more of any polymorphic alleles is

greater than a person who is not a carrier (page 9 of response). The specification more clearly is directed to the probability of individuals who carry one or more of these polymorphic alleles to be more likely affected than unaffected. This argument has been thoroughly reviewed, but is not found persuasive because there is no evidence that supports the use of these individual polymorphisms as surrogates for a HH gene mutation.

The response asserts that the "requirement that an association of SNPs at the recited positions with any particular disease or condition" is not pertinent since the specification teaches that the markers are surrogate markers predictive of the likely presence of the HH gene mutation 24d1. This argument has been reviewed but is not convincing because, as discussed above, there is no evidence that the polymorphic markers are surrogate markers. Thus, another enabling use for the polynucleotides is required. The rejection asserts that there is no association, so this can not be the enabling use for the nucleic acids.

The response acknowledges the enablement of polynucleotides which span SNPs 35983 and 61465. This enablement is supported by the specification in the individual analysis provided on page 27-29. It is well established that the relationship between polymorphisms is such that the presence of one is independent of the others. The information regarding one allele does not provide any guidance to the use or association of any other allele. Thus, analysis related to two particular SNPs does not provide analysis and enablement for any additional SNPs. The specification has not provided any evidence that all of the polymorphisms are in linkage disequilibrium or that

they are all surrogates. The fact that the alleles at the recited SNPs are relatively rare in random chromosomes does not enable the skilled artisan how to use the claimed invention.

The response asserts that the Wands factors of the predictability or unpredictability of the art and state of the art favor that practice of the instant claims requires no undue experimentation (Page 11 of response). This argument has been thoroughly reviewed, but is not found persuasive because it is unpredictable whether these polymorphisms within polynucleotides are surrogate markers for a known HH gene mutation. As provided in the rejection above, significant experimentation is required to establish that mutations are associated with diseases. The experiments often fail upon replication. It is unpredictable, absent any evidence that the claimed polynucleotides comprising polymorphisms would be useful to detect a mutation at 24d1. Thus, weighing the evidence of record, it would require undue and unpredictable experimentation to use the claimed polynucleotides.

The response asserts that since two polymorphisms are in fact found more in hemochromatosis patients, there is no reason to think that any of the other recited SNPs would not likewise be enriched in hemochromatosis patients or be indicators of a mutation. This argument has been thoroughly reviewed, but is not found persuasive because, as provided in the post filing date art, Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-

value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease. Thus, the evidence of record suggests that not all SNPs within the same gene are associated with the same disease. Thus, the arguments made by the response do not appear to be supported by evidence.

The response asserts that each of the possible bases are present at SNP 35983 and would be useful. This argument has been thoroughly reviewed, but is not found persuasive because not each of the bases have been shown to exist in nature on the sense strand. That is while A and G appear on the complement to the wild-type and variant, A and G do not appear on the sense strand. Thus, It is further unpredictable as to whether the A and G on the sense strand are useful for any particular use.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 49, and newly amended Claims 123, are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796, December 12, 1995).

Brennan teaches oligonucleotides having 10 nucleotides each (10-mers). Specifically, Brennan states, "the array contains oligonucleotides having 10 nucleotides each (10-mer)" (col. 9, lines 48-50). The oligonucleotides represent every possible permutation of the 10-mer oligonucleotide.

With respect to Claim 123, the 10-mers of Brennan are oligonucleotides that hybridize to a target comprising at least 8 consecutive bases of SEQ ID NO: 2. Under the appropriate high enough stringency conditions, these oligonucleotides which differ by a base will not hybridize to SE QID NO: 1. Therefore, Brennan teaches every possible 10-mer nucleic acid.

Response to Arguments

The response traverses the rejection. The response asserts, that Brennan does not teach or suggest an array with every possible 10-mer (page 14 of response filed June 23, 2004). The response asserts that "it is clear that an 'element' is a trimer since Brennan refers to Figure 1. This argument does not appear to be supported by the plain language of Brennan. Brennan specifically states that "with a six minute chemistry cycle time, the apparatus can produce 10-mer array plates at the rate of 1 plate or 10,000,000 oligonucleotides per hour (col. 9, lines 10-12). Additionally, Brennan clearly states that "the array contains oligonucleotides having 10 nucleotides each (10-mers)." Moreover, "the total array represents every possible permutation of the 10-mer oligonucleotide." It is clear from the plain language reading of Example 4 that the

elements on the 10-mer array are oligonucleotides of 10 nucleotides. To read each of these passages in any other way would not be considering the text of the language as plainly written.

The response states that "it is clear that an 'element' is a trimer." This argument has been thoroughly reviewed, but is not found persuasive because Brennan does not say that each element is a trimer. Rather, it is clear that the oligonucleotide has 10-mers, so it would follow that each element is a 10-mer.

The response asserts that because the "pattern of binding is assessed and the nucleotide of the probe nucleic acid is determined by ordering the nucleotide sequence according to the known sequences of the oligonucleotide elements, as shown in Figure 1," Brennan does not teach 10-mers. This argument has been thoroughly reviewed, but is not found persuasive because the interpretation suggested by the response does not appear to be read in context. The interpretation that would make sense with respect to Brennan's reference to Figure 1 which illustrates the trimer sequences, is that the ordinary artisan would apply the same assembly depicted in Figure 1 to the 10-mers. This would allow bigger sequences to order along a target rather than the little 3-mers.

With respect to applicant's arguments directed to ATTCTTGTTA (page 14 of response filed June 23, 2004), a brief and cursory review of the sequence listing and the polymorphisms, this particular 10-mer does not appear to be within the scope of the claims.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 53-54, 100, 103-104, 110-112, 114, 116-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brennan (US Patent 5,474,796, December 12, 1995) in view of Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995).

Because no patentable weight is given to the written material in the instructions describing a method, the claim is obvious in view of Brennan and Ahern. In the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "Whether the statement of intended use appears merely in the claim or in a label on the product is

immaterial so far as the question of patentability is concerned." The instructions of the instant kit are not considered to distinguish the claimed kits over the prior art.

Brennan teaches oligonucleotides having 10 nucleotides each (10-mers). Specifically, Brennan states, "the array contains oligonucleotides having 10 nucleotides each (10-mer)" (col. 9, lines 48-50). The oligonucleotides represent every possible permutation of the 10-mer oligonucleotide. Therefore, Brennan teaches every possible 10-mer nucleic acid. The oligonucleotides are identical to the claimed oligonucleotides, therefore they would hybridize under stringent conditions to the claimed oligonucleotides (limitations of Claim 100). Moreover, these primers may serve as amplification or sequencing primers (limitations of Claims 103-104). Claim 110-111 is drawn to a kit which is "configured to detect two or more SNPs. The array of Brennan is synthesized to that each oligonucleotide may be detected. With respect to Claim 112, 114, 116-119, the oligonucleotides of Brennan comprise at least 8 consecutive bases that span one of the SNPs.

Brennan does not specifically teaches packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Brennan with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Brennan into a kit, as taught by Ahern for the express purpose of saving

time and money. Therefore placing the array of Brennan into a kit would have been obvious at the time the invention was made.

Response to Arguments

The response traverses the rejection. The response asserts, that Brennan does not teach or suggest an array with every possible 10-mer (page 14 of response filed June 23, 2004). The response asserts that "it is clear that an 'element' is a trimer since Brennan refers to Figure 1. This argument does not appear to be supported by the plain language of Brennan. Brennan specifically states that "with a six minute chemistry cycle time, the apparatus can produce 10-mer array plates at the rate of 1 plate or 10,000,000 oligonucleotides per hour (col. 9, lines 10-12). Additionally, Brennan clearly states that "the array contains oligonucleotides having 10 nucleotides each (10-mers)." Moreover, "the total array represents every possible permutation of the 10-mer oligonucleotide." It is clear from the plain language reading of Example 4 that the elements on the 10-mer array are oligonucleotides of 10 nucleotides. To read each of these passages in any other way would not be considering the text of the language as plainly written.

The response states that "it is clear that an 'element' is a trimer." This argument has been thoroughly reviewed, but is not found persuasive because Brennan does not say that each element is a trimer. Rather, it is clear that the oligonucleotide has 10-mers, so it would follow that each element is a 10-mer.

The response asserts that because the "pattern of binding is assessed and the nucleotide of the probe nucleic acid is determined by ordering the nucleotide sequence

according to the known sequences of the oligonucleotide elements, as shown in Figure 1," Brennan does not teach 10-mers. This argument has been thoroughly reviewed, but is not found persuasive because the interpretation suggested by the response does not appear to be read in context. The interpretation that would make sense with respect to Brennan's reference to Figure 1 which illustrates the trimer sequences, is that the ordinary artisan would apply the same assembly depicted in Figure 1 to the 10-mers. This would allow bigger sequences to order along a target rather than the little 3-mers.

With respect to applicant's arguments directed to ATTCTTGTTA (page 14 of response filed June 23, 2004), a brief and cursory review of the sequence listing and the polymorphisms, this particular 10-mer does not appear to be within the scope of the claims.

The response asserts that Claims 100 and 123 have been amended to require at lest 18 bases. This argument has been thoroughly reviewed, but is not found persuasive because the claims are directed to at least 8 bases, not 18 bases. Thus, applicant's arguments are not commensurate with the rejected claims.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

13. Claims 100, 103-106, 123 are rejected under 35 U.S.C. 102(b) as being anticipated by Kreitman et al. (EP 0615976A1, September 21, 1994).

With regard to the limitation that the kits contain instructions, the inclusion of instructions is not considered to provide a patentable limitation on the claims because the instructions merely represent a statement of intended use in the form of instructions in a kit. See In re Ngai, 367 F.3d 1336, 70 U.S.P.Q.2d 1862 (Fed. Cir. 2004)(holding that an inventor could not patent known kits by simply attaching new set of instructions to that product).

Kreitman et al. (herein referred to as Kreitman) teaches a nucleic acid sequence encoding a lepidopteran sodium channel. SEQ ID NO: 2 comprises TTCTGCACCTTA (nucleotides 528-540). These 12 nucleotides are 100% identical to SEQ ID NO: 2 (nucleotides 35931-35942) of the instant application. Therefore, SEQ ID NO: 2 of Kreitman would hybridize to the target sequence of 12 bases of the instant application which span 35983. The oligonucleotides of Kreitman is greater than 8 bases. The oligonucleotides will not hybridize to the full length of SEQ ID NO: 1. Kreitman further teaches placing a labeled probe comprising a nucleic acid fragment into a kit (limitations of Claim 105-106). Kreitman further teaches including PCR primers (page 6, lines 38-48). These primers would function to both sequence and amplify, thus would both be amplification and sequencing primers (limitations of Claim 103-104). With respect to Claim 123, the oligonucleotide taught by Kreitman hybridizes under stringent conditions to a target comprising the 12 nucleotides that are 100% complementary to SEQ ID NO: 2 (nucleotides 35931-35942) of the instant application. SEQ ID NO: 2 of Kreitman and SEQ ID NO: 1 of the instant application will not hybridize under stringent conditions.

Therefore since Kreitman teaches every limitation of the claimed invention, Kreitman anticipates the claimed invention.

Conclusion

14. No claims allowable.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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J. Goldberg

Jeanine Goldberg
Patent Examiner
September 15, 2004